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Height at diagnosis and birth-weight as risk factors for osteosarcoma

Lisa Mirabello[1], **Ruth Pfeiffer**[1], **Gwen Murphy**[1], **Najat C. Daw**[2], **Ana Patiño-Garcia**[3], **Rebecca J. Troisi**[1,4], **Robert N. Hoover**[1], **Chester Douglass**[5], **Joachim Schüz**[6,7], **Alan W. Craft**[8], and **Sharon A. Savage**[1]

[1]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland, USA

[2]Department of Oncology, St Jude Children's Research Hospital, and Department of Pediatrics, University of Tennessee, College of Medicine, Memphis, Tennessee, USA

[3]Laboratory of Pediatrics, Pediatric Oncology Unit, Department of Pediatrics, University Clinic of Navarra, Pamplona, Spain

[4]Department of Community and Family Medicine, Dartmouth Medical School, Lebanon, New Hampshire, USA

[5]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, USA

[6]Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark

[7]Institute of Medical Biostatistics, Epidemiology and Informatics, Johannes Gutenberg-University of Mainz, Germany

[8]Department of Child Health, University of Newcastle upon Tyne, Newcastle upon Tyne, United Kingdom

Abstract

OBJECTIVES—Osteosarcoma typically occurs during puberty. Studies of the association between height and/or birth-weight and osteosarcoma are conflicting. Therefore, we conducted a large pooled analysis of height and birth-weight in osteosarcoma.

METHODS—Patient data from 7 studies of height, and 3 of birth-weight were obtained, resulting in 1067 cases with height and 434 cases with birth-weight data. We compared cases to the 2000 US National Center for Health Statistics Growth Charts by simulating 1000 age and gender matched controls per case. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for associations between height or birth-weight and risk of osteosarcoma for each study were estimated using logistic regression. All of the case data were combined for an aggregate analysis.

RESULTS—Compared to average birth-weight subjects (2665–4045g), individuals with high birth-weight (≥4046g) had an increased osteosarcoma risk (OR 1.35, 95%CI 1.01–1.79). Taller than average (51^{st}–89^{th} percentile) and very tall individuals (≥90^{th} percentile) had an increased risk of osteosarcoma (OR 1.35, 95%CI 1.18–1.54, and OR 2.60, 95%CI 2.19–3.07, respectively; P_{trend} <0.0001).

Address correspondence to: Lisa Mirabello, PhD, 'Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, 6120 Executive Blvd., EPS/7101, Rockville, MD 20892; Phone: 301- 451-9732; Fax: 301- 496-1854; mirabellol@mail.nih.gov.

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CONCLUSIONS—This is the largest analysis of height at diagnosis and birth-weight in relation to osteosarcoma. It suggests that rapid bone growth during puberty and *in utero* contributes to OS etiology.

Keywords

osteosarcoma; height; birth-weight; meta-analysis; epidemiology

INTRODUCTION

Osteosarcoma (OS) is the most common malignant bone tumor among children and adolescents [1–3], but understanding of its etiology and risk factors is limited. Therapeutic radiation and certain chemicals are associated with OS [4]. It also occurs more frequently in individuals with Paget's disease [5], and in several inherited cancer predisposition syndromes, such as Li-Fraumeni syndrome [6], hereditary retinoblastoma [7], Diamond Blackfan anemia [8], and Rothmund-Thomson Syndrome [9]. However, in the majority of OS cases there is no known predisposing factor.

OS incidence has a bimodal age distribution, with a primary peak during adolescence and a smaller, secondary peak in the elderly [10–12]. In young patients, OS occurs most frequently at sites of rapid bone growth (*e.g.*, the metaphyses of long bones). Its incidence is higher in males, and the peak incidence occurs earlier in females than males, corresponding to the pubertal growth spurt [10]. OS incidence patterns suggest that perinatal factors, as well as growth and development may have a role in etiology [13, 14]. Evidence from animals supports this theory in that OS is more common in large dog breeds, who have a 185-fold increased risk of OS compared with small dog breeds [15, 16]. This is consistent with the hypothesis that rapid and/or sustained bone growth is associated with carcinogenesis.

An association between taller stature and risk of developing OS was first suggested in 1967 [17]. Subsequently, an association with higher birth-weight has also been suggested [18]. To date, the published data investigating the relationship between height and birth-weight and OS risk are contradictory [17–34]. There have been several studies investigating the relationship between height and OS, and approximately half found that OS patients are taller than average [17, 19–25]. One study suggested an association between high birth-weight and OS [18], but four others did not [20, 31, 33, 34]. In an attempt to better understand its etiology, we conducted pooled and meta-analyses of height at diagnosis and birth-weight as risk factors of OS.

METHODS

Search protocol and data collection

Birth-weight—We performed a systematic literature search of PubMed, Embase, ISI Web of Knowledge, and MEDLINE through 2008 using combinations of the search terms "osteosarcoma" or "bone cancer" and "birth-weight". In addition, primary and review articles were reviewed for reference to additional relevant studies. We identified 5 published studies [18, 20, 31, 33, 34] that investigated the association between birth-weight and OS. We reviewed each of these studies in detail.

Hartley et al. [33] presented only median birth-weight values for OS cases and controls. Gelberg et al. [20] estimated ORs for birth-weight using matched and unmatched controls with two birth-weight groupings: <2500g (referent) compared to ≥2500g; and, 1984–2977g (referent), 2978–3313g, 3314–3664g, and 3665+g. Buckley et al. [31] estimated ORs using

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the following birth-weight groupings: 0–2700g (referent), 2800–3200g, 3200–3600g, and 3700g+. Troisi et al. [18] presented ORs with the birth-weight groupings <3000g, 3000–3499g (referent), 3500–3999g, and 4000g+. Schüz and Forman [34] (re-analyzing a study previously published [35]) estimated ORs for all bone cancers (not only OS) in two ways: (1) using birth-weight by gestational age with birth-weight categories based on the distribution of the comparison population, <10% percentile and >90% percentile for small- and large-for-gestational age, respectively; and (2) based on low and high birth-weight defined as <2500g and high as >4000g, compared to normal.

As one study published only median values and those that published ORs categorized birth-weight differently and used variable referent groups, we could not use them in a meta-analysis that combined ORs. Therefore, all of the published study groups were contacted in an effort to collect their individual patient data. We obtained birth-weight data from the primary investigators of 2 published studies (Troisi et al. [18] and Schüz and Forman [34]) and an unpublished case dataset from St. Jude Children's Research Hospital. The published studies also had control data: Troisi et al. [18] had 130 controls and Schüz and Forman [34] had 2949 controls. This resulted in 434 OS cases with birth-weight data.

The unpublished birth-weight data from St. Jude Children's Research Hospital included children with newly diagnosed osteosarcoma admitted to the St. Jude Children's Research Hospital between February 1966 and November 2006. The sex distribution was 45.9% girls and 54.1% boys.

Height at diagnosis—We performed a systematic literature search of PubMed, Embase, ISI Web of Knowledge, and MEDLINE through 2008 using combinations of the search terms "osteosarcoma" or "bone cancer" and "height" or "stature". Additionally, primary and review articles were reviewed for reference to additional relevant studies. We identified 16 published studies that investigated the association between height and OS.

Fourteen published studies only estimated height percentiles, mean height, and/or standard deviation scores (SDS) [17, 19, 21–32]. Gelberg et al. [20] estimated ORs using matched and unmatched controls for height 1 year pre-diagnosis with the following height percentile groupings: 0–32.07% (referent), 32.08–59.63%, 59.64–86.38%, and 86.39–100%. Troisi et al. [18] estimated ORs for height with <51st percentile (referent), 51–81, and >81st percentile categories.

The majority of studies did not publish ORs, and one of the two that published ORs used height 1 year prior to diagnosis. In addition, height percentiles were categorized differently. Therefore, we could not use these studies in our meta-analysis of height at diagnosis that combined ORs. We contacted all the published study groups in an effort to collect their individual patient data. Most of the older studies had since destroyed their data files. We obtained height at diagnosis data from the primary investigators of 4 published studies (Pui et al. [29], Ruza et al. [22], Cotterill et al. [23], and Troisi et al. [18]) and 2 unpublished case datasets from St. Jude Children's Research Hospital and University Clinic of Navarra, Spain. Scranton et al. [19] provided the individual data on height at diagnosis, age and gender of 43 OS patients in their published report, so these data were also included in our collection of published datasets. Only one study had control data of height: Troisi et al. [18] had 139 controls with height data. We collected a total of 1067 OS cases with data on height at diagnosis.

For the unpublished data from the University Clinic of Navarra, cases were Spanish individuals with newly diagnosed osteosarcoma who were treated at the Department of Pediatrics of the University Clinic of Navarra, Spain, from September 2000 to March 2009

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[described in 22]. The mean age of the patients at diagnosis was 15.6 (6.1) years and the sex distribution was 42.2% girls and 57.8% boys. Standing height was measured with a Harpender stadiometer (Holtain Ltd., Crymych, UK) by a trained operator.

The unpublished case data from St. Jude Children's Research Hospital included children under age 18 years with newly diagnosed osteosarcoma admitted to the St. Jude Children's Research Hospital between January 1985 and October 2007. The mean age of the patients was 13 (3.4) years and the sex distribution was 49.5% girls and 50.5% boys.

Statistical methods

We present results for the association of birth-weight and height at diagnosis with OS based on patient data collected from each study group analyzed individually, and combined for an aggregate analysis, with adjusted logistic regression models.

Birth-weight—We created a reference control population that represented the distribution of birth-weight in the general population and was comparable across studies using the 2000 U.S. National Center for Health Statistics growth standards [36]. These data were based on a collection of 5 surveys (National Health Examination Survey II and III, National Health and Nutrition Examination Survey I, II, and III) conducted from 1963 to 1994 [36]. For each case, data on birth-weight for 1000 controls were generated from a normal distribution with mean and standard deviations from the respective standard for gender for analysis of birth-weight. This control population was combined with cases of each study [including Troisi et al. [18] and Schüz and Forman [34] cases] and also used in an aggregate analysis.

Logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CI) for the association between birth-weight and risk of OS for each individual study, adjusting for gender. Race was not a confounder and thus was excluded from the model. Low and high birth-weight values were defined based on the simulated reference control distribution, the lowest 10% (≤2664 g) and highest 10% (≥4046 g) for low and high birth-weight, respectively. Average birth-weight (2665–4045g) was the referent group, and individual study cases were compared to the reference standard controls. We also analyzed all of the data including the controls from Troisi et al. [18] and Schüz and Forman [34].

All of the individual case and reference control data were combined for an aggregated analysis. For this analysis, logistic regression models were used to estimate ORs and 95% CI for the association between birth-weight and risk of OS for all case data obtained compared to the reference standard controls, adjusting for study population and gender.

Height at diagnosis—SDS were estimated for height at diagnosis, calculated as a person's actual height minus the mean height of the appropriate reference population for that age and gender divided by the reference standard deviation. Reference populations were those cited in each individual study. Unpublished data from St. Jude Children's Research Hospital, USA were compared to the 2000 U.S. National Center for Health Statistics Growth Charts [36]; and unpublished data from the Department of Pediatrics, University Clinic of Navarra, Spain were compared to the standards published for Spanish children [37]. Mean SDSs for cases were compared to the expected value for the general population (SDS = 0) using t-tests.

All but one study collected only case information, therefore, we created a reference control population that represented the distribution of height in the general population and was comparable across studies using the 2000 U.S. National Center for Health Statistics growth standards [36]. For each case, data on height for 1000 controls were generated from a normal distribution with mean and standard deviations from the respective standard for

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gender and age for analysis of height at diagnosis. This control population was combined with cases of each individual study (including Troisi et al. [18] cases) and also used in an aggregate analysis.

Logistic regression models were used to estimate ORs and 95% CI for the association between height at diagnosis and risk of OS for each individual study, adjusting for gender and age. Race was not a confounder and thus was excluded from the model. Height (in centimeters) was converted to percentile of height for a person's age and gender using 2000 U.S. National Center for Health Statistics Growth Charts [36]. Persons were defined as "taller than average" if they were in the 51^{st} to 89^{th} percentile of height for their age and gender, and they were defined as "very tall" if they were in the 90^{th} or greater percentile of height. "Average or below average height" (defined as $\leq 50^{th}$ percentile of height) was used as the referent group.

All of the individual case and reference control data were combined for an aggregated analysis. For this analysis, logistic regression models were used to estimate ORs and 95% CI for the association between height at diagnosis and risk of OS for all case data obtained compared to the reference standard controls, adjusting for study population, age, and gender.

We also combined study specific ORs for height and birth-weight estimated from the studies that provided us with individual-level data using random-effects models for a meta-analysis [38]. Heterogeneity between studies was tested with the I^2 statistic [39]. The influence of each individual study on the overall effect was evaluated by re-computing the meta-analytic estimates after omitting one study at a time. A funnel plot, and Begg's and Egger's statistical tests were used to evaluate publication bias [40, 41]. Additional published data could not be included in the meta-analysis due to the inconsistencies in their analysis methods (described above).

All analyses were also performed after stratifying by gender. Statistical analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC) and STATA version 10.1 (StataCorp, College Station, Texas) software.

RESULTS

Table 1 summarizes the 18 published studies that investigate the relationship between height and/or birth-weight and OS [17–34]. We collected data from 6 of these studies, and compiled a dataset of 1067 OS cases with data on height at diagnosis and 434 with data on birth-weight (Table 2). The age range of the cases with height data was 3–64 years (mean age = 15.6, standard deviation = 6.3; median age = 15.0). The majority of OS cases were adolescents, 93.3% were ≤25 years of age, and only 0.4% of cases were over age 40 years (Supplemental Figure 1 shows the age distribution by gender). As we expected, 57% of the OS cases were male and 43% female. Of the studies with race data (Scranton et al. [19] and Cotterill et al. [23] did not have race data; although personal communication with Cotterill et al. [23] stated the majority were Caucasian), 79.8% of cases were White, 15.7% Black, and 4.5% Other (including all other race designations).

Birth-weight as an osteosarcoma risk factor

The average birth-weights by gender for each study are shown in Table 3, and were similar to the 2000 U.S. National Center for Health Statistics standards (females 3290g [SD 520]; males 3410g [SD 550]) [36]. Males had a higher average birth-weight than females, with the exception of the unpublished data collected from St. Jude Children's Research Hospital where males had a lower average birth-weight. Since gender had a significant effect on birth-weight in all studies, it was adjusted for in the regression models. We found a

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significant association between increased risk of OS and high birth-weight (≥4046g), compared to those of average birth-weight (2665–4045g), for two of the three studies, and a marginally increased risk in an aggregated analysis (OR 1.35, 95% CI 1.01–1.79; Table 4). Males with low birth-weight tended to have an increased risk of OS, but none of the individual studies or aggregated analysis results were statistically significant; females with high birth-weight had an increased risk in two of the three individual studies, and the association was statistically significant in one study (Troisi et al. [18]: OR 1.87, 95% CI 1.00–3.51) and marginally insignificant in the aggregate analysis (Supplemental Table 1). Individual study and aggregate ORs with and without the controls from Troisi et al. [18] and Schüz and Forman [34] were nearly identical (data not shown).

Tall stature as an osteosarcoma risk factor

Both male and female patients with OS were significantly taller at diagnosis than the reference population overall, and in each individual study using SDS (Table 3). Age and gender had a significant effect on height in each study and were adjusted for in the regression models. Five individual studies showed a statistically significant increased risk of OS associated with very tall stature (≥90th percentile of height), and two studies suggested an increased risk but the associations were not statistically significant (Table 5). In the aggregated analysis we found a statistically significant increased risk of OS associated with being taller than average (51–89th percentile of height; OR 1.35, 95% CI 1.18–1.54) and very tall (≥90th percentile of height; OR 2.60, 95% CI 2.19–3.07) ($P_{trend} < 0.0001$), compared to those of average or below average height (≤50th percentile of height). Results were similar by gender, with slightly stronger associations observed in males (aggregate analysis, OR for ≥90th percentile of height: 2.84, 95% CI 2.28–3.53) than females (aggregate analysis, OR for ≥90th percentile of height: 2.28, 95% CI 1.74–2.99) (Supplemental Table 2). In an aggregated analysis restricted to 18 years of age or younger, the associations were slightly stronger (OR for ≥90th percentile of height: 2.88, 95% CI 2.39–3.46), as well as when stratified by gender (males, OR for ≥90th percentile of height: 3.13, 95% CI 2.47–3.97; females, OR 2.50, 95% CI 1.87–3.36) (all $P_{trend} < 0.0001$) (data not shown).

For both height and birth-weight, ORs from the meta-analysis were very similar to the ORs obtained from the aggregate data analysis (Supplemental Figures 2 and 3). While there was no significant heterogeneity of individual study ORs for birth-weight, (I^2, $P = 0.22$), there was significant heterogeneity of individual study ORs for height (I^2, $P < 0.001$), specifically for the very tall subcategory (≥90th percentile of height). Stratifying by gender showed that the height heterogeneity was only observed for males. Funnel plots (Supplemental Figure 4) and Begg's and Egger's statistical tests indicated no substantial publication bias (all $P > 0.05$). Influence analyses additionally showed very little variation and demonstrated that no individual study was contributing more to influence the results (data not shown).

DISCUSSION

Association studies of the relationship between stature and/or birth-weight and OS have produced inconsistent results. However, the fact that the primary peak of OS incidence occurs during and shortly after the pubertal growth spurt suggests that factors affecting bone growth could contribute to OS risk. We collected height at diagnosis and birth-weight data from six published studies and unpublished data from two centers, thus creating the largest OS case series to date. The birth-weight analyses suggested a trend towards increased risk of OS with high birth-weight which was significant in the aggregate analysis, particularly in females. Our aggregate dataset of over a thousand cases strongly confirms an association between tall stature and OS risk. A significant association between being taller than average,

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particularly for very tall individuals, and OS was consistently found in both males and females.

Previously, high birth-weight was associated with an increased risk of OS in one study [18], but it was not associated with OS in four others [20, 31, 33, 34]. Troisi et al. [18] published that those with high birth-weight (≥4000g) had a significantly increased risk of OS (OR 3.9, 95% CI 1.7–10), although there was no trend in risk with increasing weight. Another large case-control study investigating the relationship between birth-weight and OS risk found a non-significant positive association for those with the highest birth-weight (≥3700g; OR 1.39) [31] similar to the association we observed between high birth-weight and OS (OR 1.35). The other studies [20, 33, 34] that did not observe any associations with birth-weight may have been underpowered to detect this association. Overall, our data indicates a marginally statistically significant association between high birth-weight and OS risk. We did observe differences by gender; there was a statistically significant association with high birth-weight in females, while we found no association in males. However, this finding could also be due to chance.

High birth-weight is a risk factor for other childhood cancers, including acute lymphoblastic leukemia (ALL) [34, 42], primary brain tumors [43], neuroblastoma [44], rhabdomyosarcoma [45], and Wilms' tumor [46, 47]. Interestingly, recent studies of childhood leukemia and of Wilms' tumor also found an increased risk only in females with high birth-weight [47, 48]. The biological mechanism for this gender difference is unclear. Maternal factors could affect prenatal weight gain, in particular, maternal diabetes mellitus is known to lead to an excess of weight gain *in utero* and thus increased birth weight [49]. An excess of growth factors may play a role in higher birth weights; IGFs have been suggested to play a role in fetal growth and cancer [50–52], and IGF1 has been shown to be positively associated with birth weight [53]. Other proposed mechanisms to explain the increased cancer risk with high birth-weight include an altered immune function [54] and imprinting errors (loss could affect growth and have differential sex effects) [55]. High birth weight is also associated with several adult cancers [56–58]. The latency period from exposure to cancer development can vary significantly. It is plausible that pre-natal exposures and a resultant high birth weight exposes the individual to additional growth factors and, if an additional trigger is present (i.e., DNA damage or an environmental exposure), this can lead to the development of cancer later in life.

Fraumeni [17] first suggested that the development of OS in children and adolescents was related to tall stature and skeletal growth using epidemiologic data. Most subsequent studies investigating the relationship between height and OS had small numbers of patients, small or inadequate control groups, and limited statistical power. These factors could contribute to the inconsistencies seen in the OS literature. For example, some studies found that OS patients are not taller than average for their age and gender [18, 26–32], while others have suggested that patients are significantly taller than average [17, 19–25]. Two recent cohort studies with a large number of cases showed that OS patients were significantly taller at diagnosis than the reference population [23, 24]. The case-control study by Troisi et al. [18] found that height was not associated with OS risk; however, after examination of data from that study we found that the control group was significantly taller than the general population, with a SDS of 0.47, which likely contributed to the observed null association. Gelberg et at. [20] found that those with the tallest height 1-year pre-diagnosis (defined as 86.4 to 100th percentile of height) had a significantly increased risk of OS with an OR of 2.68 (95% CI 1.14–6.30; P_{trend} = 0.01), which is very similar to our finding for the tallest individuals (≥90th percentile of height; OR 2.60). We observed significant heterogeneity among studies of height, indicating the need for larger, high-quality studies to provide reliable estimates of association.

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OS incidence peaks in adolescence by gender around puberty, and the age-incidence curves closely resemble the growth velocity curves for height [59, 60]. The OS cases in our study had very similar age and gender distributions to previously published data. The greater incidence in males (male to female ratio of 1.34:1 in young adults) [10] and the typical occurrence of OS in the metaphyses of lower long bones (approximately 75% in young adults) [10] may reflect greater rates of growth [61]. The incidence peak in adolescence is followed by a rapid decline and a plateau when bone growth is complete, after age 24 years [62]. These incidence patterns are observed worldwide [63], and suggest that the biologic mechanism is present during the period of growth.

Our data supporting the hypothesis that rapid bone growth contributes to OS risk in humans are further supported by the strong positive association between OS in canines and greater breed height [64]. Rapidly growing tissue is known to be highly susceptible to carcinogenesis [65]. This risk could be due to rapidly proliferating osteogenic cells resulting in increased vulnerability to oncogenic agents, development of mitotic errors, chromosome rearrangement or neoplastic transformation [17]. OS incidence is highest during the expected adolescent growth spurt and puberty when endogenous sex hormones, growth hormones and IGF1 levels are at their highest, which may be involved in the pathogenesis of OS. Insulin-like growth factors play critical roles in carcinogenesis, and genetic variation in growth genes (*e.g.*, insulin-like growth factor 2 receptor) have been reported to be associated with increased risks of OS [66–68].

We assessed the correlation between birth-weight and height in the two studies with these data from the same individuals and found a positive correlation only among males from Troisi et al. [18]. In sensitively analyses using the Troisi et al. [18] study that mutually adjusted for height and weight this correlation did not significantly affect our effect estimates. A limitation of our study is the variation in OS diagnoses and birth time-periods, and population origin. The studies with height data were conducted between 1951 and 2008, and included individuals from the U.S., Spain, and U.K. Our findings are not likely artifacts of changing height over time as our reference standard covers most of this time period. The effects of country are also likely to be small since the SDS based on the standard population referenced by each study (Table 3) and on the 2000 U.S. National Center for Health Statistics growth standards were very similar (±0.05) for Spain and U.K. case data. Birth-weight data were collected between 1966 and 2006, and included births in the U.S. and Germany. The unpublished case data collected by St. Jude Children's Research Hospital from 1966 to 2006 covers an early time period. However, in analyses restricted to St. Jude Children's Research Hospital cases born 1985 or later, there was also no significant association between high birth-weight and OS (OR 0.99, 95% CI 0.52–1.92, vs. all cases OR 1.02 95% CI 0.66–1.56).

We also compared the distributions of height and birth-weight in the published and unpublished case series since the unpublished data were collected more recently than the published data to evaluate if time trends may be responsible for some of the differences observed. We found that the trend was towards higher birth-weight in the published data (15.7% of cases) compared to the unpublished data (9.8% of cases), and for height more unpublished cases were very tall (27.6% of cases) compared to the published case series (21.3% of cases). If a time trend were present, the unpublished cases should have higher birth-weights and be taller than the earlier collected case series. However, since we are seeing the reverse trend in the birth-weight data, a time trend effect on these data is unlikely. We also removed the unpublished case data from the pooled analyses and found that the results were similarly significant, for being taller than average OR 1.18 (95% CI 1.0–1.4) and very tall OR 2.27 (95% CI 1.9–2.8); and, for low and high birth-weight the ORs were

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0.82 (95% CI 0.5–1.4) and 1.78 (95% CI 1.2–2.6) without the unpublished data, respectively.

This is the largest OS case dataset and reference population studied to date. High birth-weight was associated with increased risk of OS in the aggregate analysis. Due to the different results in the study sets, larger studies are needed to further investigate the association between birth-weight and OS. We conclude that being taller than average is a significant OS risk factor. This suggests that rapid and/or sustained bone growth during puberty contributes to OS etiology. While our findings contribute greatly to our knowledge of OS etiology, more work is needed to further investigate potential associations between birth-weight and OS, and understand the physiologic mechanisms involved in predisposing individuals with tall stature and possibly high birth-weight to OS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Published studies investigating the relationship between height and/or birth-weight and osteosarcoma.

Author/Year	Age Group	Study Period	Country	N*	Study Design	Population	Ht/BW Presentation	Outcome	
								Ht	BW
Fraumeni, 1967 [17]	0–18	1945–1965	USA	85/202	case-control	hospital	percentiles, scores	S	—
Scranton et al. 1975 [19]	4–64	1951–1971	USA	54	cohort	two hospitals	Ht, percentiles	S	—
Goodman et al. 1978 [25]	6–25	1973–1976	USA	18	cohort	hospital	percentiles	S	—
Broström et al. 1979 [26]	<25	1972–1974	Sweden	19/195	case-control	registry	means, SDS	NS	—
Vassilopoulou-Sellin et al. 1985	—	1977–1983	USA	39	cohort	hospital	percentiles	NS	—
Operskalski et al. 1987 [28]	<25	1972–1982	USA	60/94	case-control	registry	percentiles	NS	—
Pui et al. 1987 [29]	<18	1962–1985	USA	150	cohort	hospital	SDS	NS	—
Hartley et al. 1988 [33]	<15	1980–1983	UK	12/146	case-control	multiple registries	medians	—	NS
Glasser et al. 1991 [30]	<15	1977–1985	USA	68	cohort	hospital	SDS	NS	—
Gelberg et al. 1997 [20]	3–24	1978–1988	USA	67 ht, 126 BW	case-control	registry	Ht percentiles, OR	S	NS
Buckley et al. 1998 [31]	<18	1982–1983	USA	152/152	case-control	registry	means (Ht), OR (BW)	NS	NS
Cool et al. 1998 [32]	≤15	1981–1994	UK	63	cohort	hospital	percentiles	NS	—
Rytting et al. 2000 [21]	<11	1978–1995	USA	30	cohort	hospital	percentiles	S	—
Ruza et al. 2003 [22]	≤18	1984–2000	Spain	58	cohort	hospital	means, SDS	S	—
Cotterill et al. 2004 [23]	3–39	1978–1997	UK	364	cohort	registry	SDS	S	—
Longhi et al. 2005 [24]	2–60	1981–2001	Italy	962	cohort	hospital	SDS	S§	—
Troisi et al. 2006 [18]	<40	1994–2000	USA	158/141	case-control	multiple hospitals	Ht percentiles, OR	NS	S
Schuz & Forman, 2007 [34]	≤14	1992–1994	Germany	94†/2,024	case-control	registry	means, OR	—	NS

*number of cases/controls; BW = birth-weight; Ht = height; OR = odds ratio; pct = percentile; SDS = standard deviation scores; NS = cases are not significantly different from the reference population; S = significant studies where cases were determined to be taller or had higher BW than the reference population;

†all bone tumor cases;

§significant association between taller than average stature in cases <18 years only (N = 555); —, no data available; *Shaded* rows are data we have acquired.

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Table 2

Studies that we obtained height at diagnosis and/or birth-weight data on osteosarcoma cases.

Author/Year	Case Population	Number of cases	
		Ht	BW
Scranton et al. 1975 [19]	Children's Hospital and Presbyterian-University Hospital of Pittsburgh, PA, USA	43	—
Pui et al. 1987 [29]	St. Jude Children's Research Hospital, TN, USA	168	—
Unpublished case data†	*St. Jude Children's Research Hospital, TN, USA*	*214*	*242*
Ruza et al. 2003 [22]	Department of Pediatrics, University Clinic of Navarra, Spain	58	—
Unpublished case data‡	*Department of Pediatrics, University Clinic of Navarra, Spain*	*64*	—
Cotterill et al. 2004 [23]	MRC Clinical Trials Unit, Cambridge and UKCCSG Data Centre, Leicester, UK	364	—
Troisi et al. 2006 [18]	Orthopaedic surgery departments in 10 USA medical centers *	156	144
Schuz & Forman, 2007 [34]	Nationwide GCCR, University of Mainz, Germany	—	48
	Total:	1067	434

Ht = height at diagnosis; BW = birth-weight; MRC = Medical Research Council; UKCCSG = United Kingdom Children's Cancer Study Group;

*medical centers: Massachusetts General Hospital, Boston, MA; Creighton University/St Joseph's Hospital and University of Nebraska, Omaha, NE; Children's National Medical Center and Washington Hospital Center, Washington, DC; University of Chicago and Rush Presbyterian St Luke's, Chicago, IL; University of Florida, Gainesville, FL; University of California, Los Angeles, CA; Cleveland Clinic, Cleveland OH; GCCR = German Childhood Cancer Registry; *italics* = unpublished data;

†patient height data was collected for cases diagnosed between 1985 and 2007, and birth-weight data for cases diagnosed between 1966 and 2006;

‡patient data was collected between 2001 and 2008

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Table 3

Anthropometric data by gender for each individual study and aggregate data.

Citation	Average BW (g)		Ht SDS	
	Males (SD)	Females (SD)	Males (SE)	Females (SE)
Scranton et al. 1975	—	—	0.229 (0.22)	0.575 (0.26) *
Pui et al. 1987	—	—	0.280 (0.11) *	0.235 (0.12)
Unpublished case data †	3295.5 (607.1)	3341.3 (549.3)	0.568 (0.11) **	0.331 (0.11) *
Ruza et al. 2003	—	—	0.409 (0.19) *	0.639 (0.23) *
Unpublished case data ‡	—	—	1.17 (0.29) **	0.832 (0.16) **
Cotterill et al. 2004	—	—	0.128 (0.08)	0.314 (0.11) *
Troisi et al. 2006	3462.4 (496.8)	3302.5 (549.3)	0.523 (0.15) **	0.332 (0.13) *
Schuz & Forman, 2007	3442.6 (724.9)	3383.2 (414.5)	—	—
Aggregate data	3368.2 (586.8)	3334.3 (532.6)	0.362 (0.05) **	0.369 (0.05) **

Ht = height at diagnosis; BW = birth-weight; SD = standard deviation; SE = standard error; SDS = standard deviation score;

† from St. Jude Children's Research Hospital, TN, USA;

‡ from University Clinic of Navarra, Spain;—, no data;

* One-sample student t-test $P<0.05$;

** One-sample student t-test $P<0.001$

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Table 4

Analysis of low and high birth-weight as osteosarcoma risk factors by individual study and aggregate data compared to a simulated reference population.

Citation	BW groups*	case *n* (%)	OR‡ (95% CI)
Troisi et al. 2006	≤2664	10 (6.9)	0.73 (0.38–1.39)
	2665–4045	109 (75.7)	1 (ref)
	≥4046	25 (17.4)	1.84 (1.19–2.85)
Schuz & Forman, 2007	≤2664	5 (10.4)	1.09 (0.43–2.80)
	2665–4045	36 (75.0)	1 (ref)
	≥4046	7 (14.6)	1.59 (0.71–3.60)
Unpublished case data†	≤2664	30 (12.4)	1.28 (0.87–1.89)
	2665–4045	188 (77.7)	1 (ref)
	≥4046	24 (9.9)	1.02 (0.66–1.56)
Aggregate data§	≤2664	45 (10.4)	1.08 (0.79–1.47)
	2665–4045	333 (76.7)	1 (ref)
	≥4046	56 (12.9)	1.35 (1.01–1.79)

*based on the birth-weight (BW) distribution in the simulated controls, low (≤2664) and high (≥4046) 10% of the control distribution;

‡odds ratio and 95% confidence intervals, adjusted for gender;

†from St. Jude Children's Research Hospital, TN, USA;

§aggregate analyses were additionally adjusted for study.

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Table 5

Analysis of height at diagnosis as an osteosarcoma risk factor by individual study and aggregate data compared to a simulated reference population.

Citation	Percentile of height	case *n* (%)	OR* (95% CI)
Scranton et al. 1975	≤50th	21 (48.8)	1 (ref)
	51–89th	16 (37.2)	0.94 (0.49–1.81)
	≥90th	6 (14.0)	1.45 (0.59–3.60)
Pui et al. 1987	≤50th	71 (42.3)	1 (ref)
	51–89th	72 (42.8)	1.25 (0.90–1.74)
	≥90th	25 (14.9)	1.76 (1.12–2.78)
Unpublished case data†	≤50th	69 (32.2)	1 (ref)
	51–89th	98 (45.8)	1.77 (1.30–2.41)
	≥90th	47 (22.0)	3.38 (2.34–4.90)
Ruza et al. 2003	≤50th	22 (37.9)	1 (ref)
	51–89th	28 (48.3)	1.56 (0.89–2.72)
	≥90th	8 (13.8)	1.90 (0.85–4.28)
Unpublished case data‡	≤50th	14 (21.9)	1 (ref)
	51–89th	33 (51.5)	2.82 (1.51–5.28)
	≥90th	17 (26.6)	6.42 (3.16–13.03)
Cotterill et al. 2004	≤50th	150 (41.2)	1 (ref)
	51–89th	146 (40.1)	1.12 (0.89–1.41)
	≥90th	68 (18.7)	2.45 (1.84–3.27)
Troisi et al. 2006	≤50th	59 (37.8)	1 (ref)
	51–89th	66 (42.3)	1.30 (0.91–1.84)
	≥90th	31 (19.9)	2.84 (1.83–4.38)
Aggregate data§	≤50th	406 (38.2)	1 (ref)
	51–89th	456 (42.9)	1.35 (1.18–1.54)
	≥90th	202 (18.9)	2.60 (2.19–3.07)

*Odds ratio and 95% confidence intervals, adjusted for age and gender;

†from St. Jude Children's Research Hospital, TN, USA;

‡from University Clinic of Navarra, Spain;

§aggregate analyses were additionally adjusted for study.